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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,428	10/14/2003	Mary Jo Mulligan-Kehoe	DC-0230	1865

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,428	MULLIGAN-KEHOE, MARY JO	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 1-5 are pending.

2. Applicant's election with traverse of Group I, Claims 1-2 drawn to a method for producing a 34 kDa truncated plasmin proteolytic protein and a truncated plasmin proteolytic protein, filed 8/25/05, is acknowledged. The traversal is on the grounds that the method set forth in the claims of Group I is distinct from that disclosed by Mulligan-Kehoe et al. While this reference teaches at page 8590 (col. 1) that urPAI-12a protein (30-120 nM) was bound to 10 nM of uPA at room temperature for l hour." And Following this reaction 33 nM of plasminogen was added to the rPAI-12a'uPA reaction mix and incubated at 370C for 20-30 min.", this reference does not teach combining plasminogen and rPAI-12a for a specified amount of time and subsequently adding uPA. The specification teaches at pages 23-29 that the order in which the reaction components are added is essential to quantity and quality of products produced. Further, the methods of Group I and II claims are linked by the use of rPAI-12a, i.e., plasminogen. Thus, there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features thereby fulfilling the requirement of unity of invention referred to in Rule 13.1. The Examiner respectfully disagrees for reasons of record as supplemented below. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. A same or corresponding technical feature shared between Group I and Group II is a 34 kDa truncated plasmin proteolytic protein. However, this same or corresponding technical feature has already been taught by Mulligan-Kehoe et al. (reference of record). As stated in the previous Office Action, Mulligan-Kehoe et al. teach a 34 kDa truncated plasmin proteolytic protein (see page 8950, col. 1, Figure 5, in particular). Further, Mulligan-Kehoe et al teach plasminogen is incubated with rPAI-123 for 1 hr at 37 °C, then uPA was added for an additional 1 hr at 37 C (see page 8590, col. 2, first paragraph, in particular). Mulligan-Kehoe et al further teach rPAI-123 cleavage of plasmin into approximately 36 and 38-kDa fragments regardless of the permutation for combining rPAI-123, uPA and plasminogen (see page 8595, col. 1, in particular). Thus, the technical feature is not special since it was known in the prior art and therefore cannot make a contribution over the prior art. Since the inventions lack the same or corresponding special technical feature, then the inventions listed as Groups I and Group II are

not so linked as to form a single general inventive concept under PCT Rule 13.1. Therefore, the requirement of Group 1 (claims 1-2) and Groups 2 is still deemed proper and is therefore made FINAL.

3. Claims 3-5 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 1-2, drawn to a method for producing a 34 kDa truncated plasmin proteolytic protein and a truncated plasmin proteolytic protein, are being acted upon in this Office Action.

5. The CFR filed 10/30/03 has been corrected by the STIC Systems Brach, specifically, invalid/beginning/end-of-file text has been deleted.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for producing a 34 kDa truncated plasmin proteolytic protein comprising combining plasminogen and porcine or human plasminogen activator inhibitor 1 lacking a partial heparin-binding domain and RCL domain ($rPAI\text{-}1_{23}$) for two hours at 37 °C and subsequently adding urokinase plasminogen activator (uPA) for an additional hour at 37 °C so that a 34 kDa truncated plasmin proteolytic protein (angiostatin) is produced and (2) a 34 kDa truncated plasmin proteolytic protein produced by said method, **does not** reasonably provide enablement for the method as recited in claim 1 and any 34 kDa truncated plasmin proteolytic protein as recited in claim 2 for treating angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for producing a 34 kDa truncated plasmin proteolytic protein (angiostatin or plasminogen kringles 1-3) comprising combining plasminogen and porcine plasminogen activator inhibitor 1 lacking a partial heparin-binding domain and RCL domain (rPAI-1_{23}) for two hours at 37 °C and then adding two-chain urokinase plasminogen activator (uPA) for an additional hour at 37 °C so that a 34 kDa truncated plasmin proteolytic protein (angiostatin) is produced (see page 14, lines 20-22, page 29). The specification discloses that the 34 kDa truncated plasmin proteolytic protein may be useful as an anti-angiogenic agent (page 29, line 28).

The specification does not teach how to make any 34 kDa truncated protein because of the following reasons. First, the incorporation of essential material rPAI-I23 in the specification by reference to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). The attempt to incorporate subject matter into this application by reference to (Mulligan-Kehoe et al, J Biol Chem 263: 9129-9141, 2001) is improper because rPAI-I23 is essential materials for the method of making the claimed product.

Second, other than the specific conditions mentioned above to produce the claimed 34 kDa truncated plasmin proteolytic protein, there is insufficient guidance as to the concentration of reactants, the duration of incubation and the temperature at which the reaction takes place to consistently producing the claimed 34 kDa truncated plasmin proteolytic protein.

Third, there is insufficient guidance as to the structure of the truncated plasmin proteolytic protein without the amino acid sequence.

Fourth, there is insufficient guidance and in vivo working example demonstrating that this 34 kDa truncated plasmin proteolytic protein has anti-angiogenic effect in vivo for a method of treating diseases related to angiogenesis.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Dermer et al teach that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapt to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference teaches that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interaction.

Gura et al teach the shortcomings of potential anti-cancer agents including extrapolating from in vitro protocols, the problems of drug testing for cancer is that the model system are not predictive at all. Given the lack of guidance and in vivo working example, it is unpredictable whether claimed 34 kDa truncated plasmin proteolytic protein is effective as an anti-angiogenic agent for treating cancer.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any and all 34 kDa truncated plasmin proteolytic protein produced by the claimed method, (2) rPAI-123, (3) uPA and (4) the condition such as time, temperature and concentration of each reactant in the claimed method.

The specification discloses only a method for producing a 34 kDa truncated plasmin proteolytic protein (angiostatin or plasminogen kringles 1-3) comprising combining plasminogen and porcine plasminogen activator inhibitor 1 lacking a partial heparin-binding domain and RCL domain (rPAI-1_{23}) for two hours at 37 °C and then adding two-chain urokinase plasminogen activator (uPA) for an additional hour at 37 °C so that a 34 kDa truncated plasmin proteolytic protein (angiostatin) is produced (see page 14, lines 20-22, page 29). The specification discloses that the 34 kDa truncated plasmin proteolytic protein may be useful as an anti-angiogenic agent (page 29, line 28).

The specification does not teach the structure associate with function of any and all 34 kDa truncated plasmin proteolytic protein, rPAI-123, and uPA without the chemical structure or amino acid sequence. Other than the specific condition used by applicant to produce the claimed 34 kDa mentioned above, the other conditions are not adequately described.

Given the lack of any additional 34 kDa truncated plasmin proteolytic protein produced by the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of plasmin proteolytic protein to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claim 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "rPAI-123" and "uPA" in claim 1 is ambiguous and indefinite because "rPAI-123" and "uPA" are merely laboratory designations which does not clearly define the structures of the products in the claimed method, since different laboratories may use the same laboratory designations to define completely distinct polypeptides.

11. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (1) the specified amount of time before adding uPA is missing in claim 1, (2) the temperature at which the reaction takes place, and (3) the concentration of each reactants.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Mulligan-Kehoe et al (J Biochemical Chemistry 276(11): 8588-8596, March 2001; PTO 892).

Mulligan-Kehoe et al teach a 34 kDa truncated plasmin proteolytic protein (see page 8595, col. 2, third full paragraph, in particular). The reference protein is due to rPAI-123 cleavage of plasmin regardless of the permutation for combining rPAI-123, uPA, and plasmin (see page 8595, col. 1, in particular). Mulligan-Kehoe et al further teach a method of making truncated plasmin proteolytic protein comprising combining plasminogen (Plg) and rPAI-123 for 1 hour at 37C, then adding uPA for an additional 1 hr at 37 C (see page 8590, col. 2, first paragraph, in particular). Given the claimed method steps are the same as that of the reference method steps, the method inherently produces the same 34 kDa truncated plasmin proteolytic protein. Thus, the reference teachings anticipate the claimed invention.

14. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,801,146 (September 1, 1998; PTO 892).

The 146 patent teaches a truncated plasmin proteolytic protein such as angiostatin containing kringles 1-3 (see col. 2, lines 17-19, in particular). The reference protein inherently has the same 34 kDa as evidenced by the specification on page 14, lines 20-22, in particular). A

product is a product, irrespective of how it is made. Thus, the reference teachings anticipate the claimed invention.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 16, 2005

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